A Randomized Phase III Trial of Postoperative Adjuvant Therapy with S-1 Alone versus S-1 plus PSK for Stage II/IIIA Gastric Cancer: Hokuriku-Kinki Immunochemo-Therapy Study Group-Gastric Cancer (HKIT-GC)

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In this randomized multicenter Phase III study, patients with curatively resected Stage II/IIIA gastric cancer were assigned to postoperative adjuvant therapy with an oral fluoropyrimidine S-1 alone (2 weeks of treatment and 1 week of rest for 6 months, followed by 2 weeks of treatment and 2 weeks of rest for 6 months) or S-1 combined with an oral biological response modifier PSK (the same regimen of S-1 plus daily PSK for 12 months). The main objective was to evaluate the survival benefit and quality of life (QOL) of combined therapy. The primary end points were the time to relapse and the duration of survival after surgery, i.e. the rates of disease-free survival and overall survival at 3 and 5 years. The secondary end points were the relations of survival rates to drug compliance, QOL, adverse events, postoperative complications, relapse status, and the preoperative expression of immune or tumor markers. The sample size was 140 per treatment arm.

Key words: gastric cancer – adjuvant chemotherapy – immunotherapy – S-1 – PSK

INTRODUCTION

Although surgery remains the standard treatment for T2–T4 resectable gastric cancer in Japan, the outcome of surgery becomes poorer with further progression of the disease. The 5-year survival rates for Stage II, IIIA and IIIB gastric cancer are ~70, 50, and 30%, respectively. Curative surgery alone is thus inadequate for advanced disease, and postoperative adjuvant therapy becomes necessary. Recently, the National Surgical Adjuvant Study Group for Gastric Cancer (N-SAS-GC) reported that postoperative adjuvant chemotherapy with UFT (tegafur and uracil; Taiho Pharmaceutical Co., Tokyo, Japan), a dihydropyrimidine dehydrogenase (DPD)-inhibitory oral fluoropyrimidine, significantly reduced the risk of relapse at 4 years in patients with T2N1 (Stage II) and T2N2 (Stage IIIA) gastric cancer (1). S-1 (TS-1; Taiho Pharmaceutical Co., Tokyo, Japan) is a second-generation DPD-inhibitory oral fluoropyrimidine designed to provide higher and more prolonged serum levels of 5-fluorouracil, as compared with UFT (2,3). In Stage II/III gastric cancer, the Adjuvant Chemotherapy Trial of S-1 for Gastric Cancer (ACTS-GC), a large industry-driven clinical trial, compared surgery alone with surgery plus S-1. The study closed the enrollment with 1059 patients at the end of 2004, and the survival results are expected to be available by 2010. This trial is expected to provide definitive proof of the efficacy of postoperative adjuvant chemotherapy with an oral fluoropyrimidine. Another large clinical trial of adjuvant treatment in patients with curatively resected gastric cancer started in...
August 2004. This trial was designed to validate the effectiveness of paclitaxel, S-1, and combined sequential treatment with these agents, as compared with UFT, used as an active control (SAMIT trial) (4).

Factors such as the quality of life (QOL) and convenience have a higher priority in patients receiving postoperative adjuvant treatment to prevent cancer recurrence than in those receiving therapy for advanced or recurrent disease. An oral formulation with a low incidence of adverse reactions will facilitate treatment on an outpatient basis. Protein-bound polysaccharide K (PSK) (KRESTIN®; Kureha Chemical Industry Co., Tokyo, Japan), an oral biological response modifier, has a completely different mechanism of action from those of cytotoxic chemotherapy agents. The actions of PSK include immunological effects such as the induction of interleukin-2 and interferon-γ, thereby stimulating lymphokine-activated killer cells, enhancing natural killer cells, and neutralizing immunosuppressive cytokines associated with surgical invasion or tumor aggressiveness (5). PSK also has direct effects on cancer cells, including induction of apoptosis, suppression of tumor infiltration and augmentation of HLA class I expression (6). Because of these unique actions, PSK is considered well suited for concurrent use with cytotoxic agents as postoperative adjuvant treatment. In fact, Nakazato et al. (7) demonstrated that the addition of PSK to adjuvant chemotherapy with mitomycin C and oral fluorouracil significantly prolonged survival after curative gastrectomy in a large prospective trial of patients with gastric cancer. In addition, postoperative adjuvant treatment with PSK in combination with UFT is effective against colorectal cancer (8). However, there has been no study of adequate size that reported the results of treatment with a combination of PSK and S-1.

This randomized Phase III trial was designed to compare S-1 alone with S-1 plus PSK, given as postoperative adjuvant treatment to patients with Stage II/IIIA gastric cancer. The major objective was to assess whether the addition of PSK to S-1 improves survival and QOL. A feasibility study of adjuvant treatment to patients with Stage II/IIIA gastric cancer demonstrated that the standard regimen of S-1 (4 weeks of treatment and 2 weeks of rest) for 1 year was feasible but associated with a slight increase in adverse reactions, probably due to the effect of gastrectomy (9). The regimen of S-1 in the present study therefore comprises 2 weeks of treatment and 1 week of rest for 6 months, followed by 2 weeks of treatment and 2 weeks of rest for the next 6 months.

PROTOCOL DIGEST OF THE STUDY

OBJECTIVE

The main objective was to evaluate whether the addition of PSK to S-1 improves survival and patients’ QOL. The study was approved by the ethics committees of Kanazawa University, Kyoto Prefectural University of Medicine, and other participating centers.

RESOURCES

The study did not receive any grants from any organization or industry. All treatment-related costs were covered by National Health Insurance. The registration center was administered by a fund from the Foundation for Promotion of Clinical Research, Kanazawa University.

END POINTS

The primary end points were the time of relapse and the duration of survival after surgery, i.e., rates of disease-free survival and overall survival at 3 and 5 years. The secondary end points were the relations of survival rates to drug compliance, QOL, adverse events, postoperative complications, relapse status, and the preoperative expression of immune or tumor markers. Immune or tumor markers include immunosuppressive acid protein (IAP), lymphocyte/monocyte ratio, lymphocyte/monocyte ratio, carcinoembryonic antigen (CEA) and carbohydrate antigen (CA) 19-9, as determined by blood testing.

ELIGIBILITY CRITERIA

Patients with resectable gastric cancer [curability A or B to according to the Japanese Classification of Gastric Carcinoma, 13th edition (2nd English edition) (10)] who satisfy the inclusion criteria and do not meet the exclusion criteria as described below are recruited as subjects.

Inclusion Criteria

1. Histologically proven, Stage II, IIIA resectable gastric adenocarcinoma.
2. Age between 20 and 80 years.
3. No preoperative cancer treatment, such as chemotherapy, immunotherapy and radiotherapy.
4. Serum IAP measured within 2 weeks before surgery.
5. No synchronous or metachronous cancers.
7. Preoperative ECOG performance status of 0–2.
8. Written informed consent.

Exclusion Criteria

1. Fresh gastrointestinal bleeding.
2. Ascites or pleural effusion.
3. Serious infectious disease.
4. Intestinal palsy or intestinal occlusion.
5. Women who are pregnant or hope to become pregnant during the study period.
6. Diabetes mellitus treated by insulin.
7. A history of ischemic heart disease.
9. Continuous treatment with steroids.
10. A medical history of allergy or hypersensitivity to any drugs.
11. Patients judged inappropriate for the study by their physicians.
REGISTRATION

Eligible patients within 42 days after operation are centrally registered and randomly assigned to treatment by the Registration Center, located at the Department of Gastroenterologic Surgery, Graduate School of Medical Science, Kanazawa University. Randomization is performed by the minimization technique. Patients are stratified according to three factors: center administering treatment, disease stage (Stage II, IIIA) and preoperative serum IAP level (cut-off value, 580 μg/ml). Accrual of patients was started in September 2005.

TREATMENT METHODS

Enrolled patients were assigned to S-1 alone (Arm A) or to S-1 plus PSK (Arm B). The medication was started between 28 days and 42 days after operation.

Arm A (S-1 alone):
S-1 80 mg/m²/day* 2 weeks of treatment and 1 week of rest for 6 months (8 cycles), followed by 2 weeks of treatment and 2 weeks of rest for 6 months (7 cycles).

Arm B (S-1 + PSK):
The same dosage of S-1 as that used in Arm A plus PSK 3 g/day** for 12 months.

* S-1 is given orally at a dose not exceeding 80 mg/m²/day in two divided doses (after breakfast and dinner), assigned according to the patient’s body surface area (BSA): BSA <1.25 m², 80 mg; 1.25–1.50 m², 100 mg; and BSA >1.5 m², 120 mg.

** PSK is given orally at a fixed dose of 3 g/day in three divided doses (after breakfast, lunch and dinner).

FOLLOW-UP

During the protocol treatment, patients undergo physical and laboratory examinations weekly or monthly. During and after finishing the protocol treatment, patients are physically examined for recurrence, and tumor markers (CEA, CA19-9, CA125 and IAP) are measured every 3 months for 3 years. Abdominal CT scans and chest radiographs are obtained every 6 months for 3 years. QOL during the treatment period is assessed by means of the QOL questionnaire ‘EORTC QLQ-STO22’ before operation; after operation (before starting the protocol treatment); and 3, 6 and 12 months after operation (5 time points) (11). Registered patients will be followed up to confirm the presence or absence of recurrence and survival status for 5 years after accrual of the last patient.

STUDY DESIGN AND STATISTICAL METHODS

The overall survival rates of arm A (S-1 alone) and arm B (S-1 + PSK) in the present study were estimated on the basis of the 5-year overall survival rates of patients with Stage II and IIIA gastric cancer in the 5-FU alone group and 5-FU + PSK group in the multicenter study conducted by Nakazato et al. (7). The overall survival rate in the S-1 group was assumed to be 5% higher than the rate achieved in the 5-FU group. Assuming that the ratio of patients with Stage II disease to those with Stage IIIA disease would be 60:40, the rate of overall survival at 5 years was estimated to be 69.5 and 84.0% for arms A and B, respectively. The number of patients required to demonstrate a significant difference in outcome between the two arms with an alpha value of 0.05 and a power of 80% was calculated to be as follows:

Arm A (S-1 alone): 133 patients
Arm B (S-1 + PSK): 133 patients

Assuming a dropout or ineligibility rate of about 5%, the target number of enrolled patients was determined to be 140 patients per arm (total, 280 patients).

NIH REGISTRATION OF THE PROTOCOL

The study protocol was registered to the clinicaltrials.gov web site of the US National Institutes of Health (identifier NCT00216034) on 18 September 2005. Details are available at the following address: http://www.clinicaltrials.gov/ct/show/NCT00216034?order=1.

PARTICIPATING INSTITUTIONS

Surgery departments of the following 48 centers in the Hokuriku and Kinki regions of Japan are participating in the trial:

Kanazawa University Graduate School of Medical Science, Kyoto Prefectural University of Medicine Graduate School of Medical Science, University of Fukui Faculty of Medicine, Shiga University of Medical Science, Aiseikai Yamashina Hospital, Akashi Municipal Hospital, Asanogawa General Hospital, Ayabe City Hospital, Ishinkai Yao General Hospital, Uji Hospital, Ohmihachiman City Hospital, Kanazawa Social Insurance Hospital, Kitade Hospital, Keijyu Medical Center Hospital, Kohinkai Ohshima Hospital, Kyoto Ohashi General Hospital, Kyoto Kizugawa Hospital, Kyoto First Red Cross Hospital, Kyoto Prefectural Yosanoumi Hospital, Saiseikai Kyoto Hospital, Saiseikai Shiga Hospital, Social Insurance Kobe Central Hospital, Social Insurance Kyoto Hospital, Daini Okamoto General Hospital, Tanabe Central Hospital, Toyama Prefectural Central Hospital, Toyama Rousai Hospital, National Hospital Organization Kanazawa Medical Center, National Hospital Organization Fukui Hospital, National Hospital Organization Maizuru Medical Center, Nara City Hospital, Nantan General Hospital, Nishijin Hospital, Higashiohmi City Gamou Hospital, Fukui Cardiovascular Center Hospital, Fukui General Hospital, Fukuchiyma City Hospital, Houju Memorial Hospital, Hoyu Hospital, Maizuru Red Cross Hospital, Matsushita Memorial Hospital, Midorigaoka Hospital, Meiji University of Oriental Medicine Hospital, Rakusai Shimizu Hospital, Rakuwakai Marutamachi Hospital, Rokujizo General Hospital, Public Central Hospital of Matto Ishikawa, JR Osaka Railway Hospital.
References


